The effect of multivalent Sonic hedgehog on differentiation of human embryonic stem cells into dopaminergic and GABAergic neurons.

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Public Summary:
Stem cell differentiation is regulated by complex repertoires of signaling ligands that often use multivalent interactions, where multiple ligands tethered to one entity interact with multiple cellular receptors to yield oligomeric complexes. One such ligand is Sonic hedgehog (Shh), whose posttranslational lipid modifications and assembly into multimers enhance its biological potency, potentially through receptor clustering. Investigations of Shh typically utilize recombinant, monomeric protein, and thus the impact of ligand clustering on its potency is unexplored. Among its many activities, Shh is required for the development of midbrain dopaminergic (mDA) and forebrain gamma-aminobutyric acid (GABA) inhibitory neurons, which are therapeutically relevant for Parkinson's Disease and epilepsy. We have designed multivalent biomaterials presenting Shh in defined spatial arrangements and investigated the role of Shh valency in the differentiation of human embryonic stem cells (hESCs) into these therapeutically important cell types. Multivalent Shh conjugates, compared to the monomeric Shh, increased the percentages of neurons belonging to mDA or forebrain GABAergic fates from 33% to 60% or 52% to 86%, respectively. Thus, multivalent Shh bioconjugates can enhance neuronal lineage commitment of pluripotent stem cells and thereby facilitate efficient derivation of neurons that could be used to treat human disease.

Scientific Abstract:
Stem cell differentiation is regulated by complex repertoires of signaling ligands which often use multivalent interactions, where multiple ligands tethered to one entity interact with multiple cellular receptors to yield oligomeric complexes. One such ligand is Sonic hedgehog (Shh), whose posttranslational lipid modifications and assembly into multimers enhance its biological potency, potentially through receptor clustering. Investigations of Shh typically utilize recombinant, monomeric protein, and thus the impact of multivalency on ligand potency is unexplored. Among its many activities, Shh is required for ventralization of the midbrain and forebrain and is therefore critical for the development of midbrain dopaminergic (mDA) and forebrain gamma-aminobutyric acid (GABA) inhibitory neurons. We have designed multivalent biomaterials presenting Shh in defined spatial arrangements and investigated the role of Shh valency in ventral specification of human embryonic stem cells (hESCs) into these therapeutically relevant cell types. Multivalent Shh conjugates with optimal valencies, compared to the monomeric Shh, increased the percentages of neurons belonging to mDA or forebrain GABAergic fates from 33% to 60% or 52% to 86%, respectively. Thus, multivalent Shh bioconjugates can enhance neuronal lineage commitment of pluripotent stem cells and thereby facilitate efficient derivation of neurons that could be used to treat Parkinson's and epilepsy patients.